REMARKS

No new amendments have been introduced in the listing of claims shown on page 2 of this paper. Claims 37-39 are currently pending and under examination.

The obviousness rejections are addressed in the order presented in the Office Action dated July 5, 2006.

Rejection of claims 37 and 38-Bonjouklian, Arnold, Volinia, and Xiao or Skorski

The Examiner has maintained the rejection of claims 37 and 38 as allegedly unpatentable over Bonjouklian in view of Arnold and Volinia and further in view of Xiao or Skorski. In brief, it is the Examiner's position that it would have been obvious to combine the teachings of the cited art to derive the current invention. The Examiner alleges that one of skill in the art would have been motivated to include ovarian tumors that were characterized by the amplification of a chromosomal region containing *PIK3CA* in the method of Bonjouklian because it was known in the art that 3q26 was amplified (Arnold) and that *PIK3CA* was found at 3q26.3 (Volinia). The Examiner contends that it would have been obvious that amplification of 3q26, which contains the *PIK3CA* locus, would result in elevated PIK3CA in ovarian cancer cells. The Examiner further argues that it would have been obvious in view of Xiao and Skorski that cancer cells that overexpress or are otherwise PI3 kinase-dependent would be sensitive to wortmannin.

In reply to the arguments submitted in Applicants previous response, the Examiner asserts that the expectation that amplification of *PIK3CA* would lead to elevated levels or PIK3CA-depndent cancer cell proliferation is provided by Bonjuoklian and Xiao and Skorski. Specifically, the Examiner alleges that one of ordinary skill in the art would reasonably expect a correlation between amplification of *PIK3CA* and an involvement in ovarian cancer cells. Applicants have traversed this rejection for reasons of record. In short, the observation that a broad region of chromosome 3q26 (*i.e.*, 3q26-qter), which contains the *PIK3CA* locus, is amplified in some ovarian tumors does not lead one of skill to the conclusion that PIK3CA is involved in ovarian cancer cell proliferation, despite the prior art involvement of *PIK3CA* in proliferation of other cancers.

To additionally address this rejection, Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 by Joe W. Gray, Ph.D. Dr. Gray explains that the fact that the broad region of 3q26-qter was known to be amplified in ovarian cancer does not lead one of skill in the art to conclude that amplification of *PIK3CA*, which is one of numerous genes located in this broad region, results in overexpression of PIK3CA and is therefore indicative of a role for PI3 kinase in oncogenesis in ovarian cancer cells that contain the amplified region.

Dr. Gray first reviews the teachings of Arnold. Arnold describes a comparative genomic hybridization (CGH) study of forty nine ovarian cancer tumors. In this CGH analysis, differentially labelled total genomic DNA from a tumor sample and from a normal reference control sample were co-hybridized to normal metaphase chromosomes. The resulting ratio of the fluorescence intensities of the probes hybridized to the chromosomes is approximately proportional to the ratio of the copy numbers of the corresponding DNA sequences in the tumor and normal reference genomes. Arnold identified the region of 3q26-qter as being increased in copy number in 42% of the ovarian tumors that were analyzed. However, Dr. Gray notes that although it was known in the art that the gene encoding the catalytic subunit of PI3 kinase (PIK3CA) is located at 3q26.3, the CGH study as performed by Arnold using metaphase chromosomes does not provide sufficient resolution to determine that the chromosomal subregion containing the *PIK3CA* locus is a focal point of amplification.

Next, Dr. Gray explains that even though a gene may be present in an amplified chromosomal region, that fact alone does not lead one of skill to conclude that a particular gene is overexpressed. Dr. Gray points out that many genes are present in chromosomal region 3q26-qter. As an example, he notes that the genome browser of the University of California, Santa Cruz shows that numerous genes are located in the 3q26 region alone. However, there is no evidence that all or even most of the products of these many genes are overexpressed in ovarian tumors.

It is Dr. Gray's opinion as a practitioner in this art for many years that although *PIK3CA* may have been of potential interest due to its biological function in proliferation or its overexpression in other cancers, at the time of the invention one of skill could not have concluded that the mere presence of the gene in this broadly amplified region would predictably

lead to a correlation with overexpression of the protein and an oncogenic role in ovarian cancer cell proliferation.

Applicants have now discovered that amplification of the particular subregion at 3q26.3, including *PIK3CA*, is of diagnostic significance for cancer and further, that amplification of *PIK3CA* is in fact associated with increased PIK3CA expression and ovarian cancer cell proliferation. In view of the foregoing, the rejection has not established a proper case of *prima facie* obviousness that the combination of art cited by the Examiner would lead one of skill to Applicants' invention. Applicants therefore respectfully request withdrawal of the rejection.

Rejection of claims 37 and 38-Bonjouklian, Daneshvar, and Xiao or Skorski

Claims 37 and 38 were additionally rejected as allegedly obvious over Bonjouklian in view of Daneshvar *et al., American Journal of Human Genetics* Vol. 59, No. 4 SUPPL., pp. A65, November 1996 ("Daneshvar ") and further in view of Xiao or Skorski. Applicants respectfully traverse this rejection.

Daneshvar was published less than a year before the priority date of the current application. Submitted herewith is a Declaration of Inventorship under 37 C.F.R. § 1.132 by Joe W. Gray and Laleh Shayesteh (formerly Daneshvar), who are also co-authors of Daneshvar. The Declaration provides evidence that to the extent that the claimed subject matter is taught or suggested by Daneshvar, it is the work of the inventors named on the present application. In view of the submission of this Declaration, Daneshvar is removed as a prior art reference. Applicants respectfully request withdrawal of the rejection.

Rejection of claim 39-Bonjouklian, Arnold, Volinia, and Xiao or Skorski in view of Powis or alternatively in view of Lavin or in view of June

The rejection of claim 39 as allegedly unpatentable over Bonjouklian, Arnold, Volinia, and Xiao or Skorski as applied to claims 37 and 38 above, and further in view of Powis, or alternatively, in view of Lavin or in view of June was also maintained. The Examiner contends that one of skill would have been motivated to use LY294002 in the methods of the invention, because it was known to be an effective inhibitor of PI3 kinase, as evidenced by any of the three secondary references. Applicants respectfully traverse this rejection for reasons of

record. The cited art (Bonjouklian, Arnold, Volinia, and Xiao or Skorski) applied to claims 37 and 38 fails to establish a proper case of obviousness for the reasons explained above. The secondary references merely teach that LY294002 is a PI3 kinase inhibitor. Such disclosure does not cure the defects in the Examiner's arguments based on the primary references. Accordingly, claim 39 is patentable over the cited art. Applicants therefore respectfully request withdrawal of the rejection.

Rejection of claim 39-Bonjouklian, Daneshvar, and Xiao or Skorski in view of Powis or alternatively in view of Lavin or in view of June

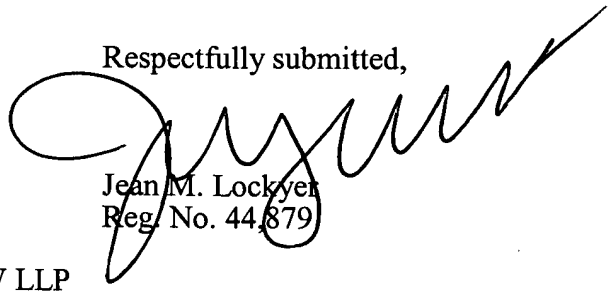
Claim 39 was also rejected as allegedly unpatentable over Bonjouklian, Daneshvar, and Xiao or Skorski as applied to the rejections of claims 37 and 38 above, and further in view of Powis, or alternatively, in view of Lavin or in view of June. Daneshvar is not available as a prior art reference in view of the submission of the Declaration of Inventorship under 37 C.F.R. § 1.132. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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